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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,909	06/08/2001	Rivka Dikstein	13005-002001	3643

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/06/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,909	DIKSTEIN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *3-5,7-11,14,17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,12,13,15,16 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 20-21, which are related to claims 1-2, 6, 12-13, 15-16, 18-19 and are not new matter.

Accordingly, claims 1-2, 6, 12-13, 15-16, 18-19 and new claims 20-21 are examined in the instant application, wherein claims 1-2, 6, 12-13, 15-16, 18-19 and new claims 20-21 are examined only to the extent of SEQ ID NO:2 and a fragment thereof.

It is noted that the modified fragment species has been withdrawn from consideration as being drawn to non-elected species.

The following are the remaining rejections.

OBJECTION

Claims 20-21 are objected to for the use of the language "corresponding to". It is not clear how the polypeptide fragment "corresponds" to amino acids 443-52 of SEQ ID NO:2.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1) Claims 1-2, 6, 13, 15-16 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a fragment of the TAFII105 polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological

activity of SEQ ID NO:2 for reasons already of record in paper No:14 . New claims 20-21 are rejected for the same reasons already of record.

Applicant submits a Declaration by Dr. Dickstein, and a reference by Yamit-Hezi et al, 1998, stating that the claimed fragment has dominant negative effect on NF-kB, and that TAFII105 polypeptide mediates activation of anti-apoptotic genes by NF-kB. Applicant further asserts that as stated in the Declaration, p65 is a subunit of the NF-kB transcriptional factor, and that the anti-apoptotic activity of NF-kB is conferred by p65.

The submission of the Declaration by Dr. Dickstein and the recitation of the reference by Yamit-Hezi are acknowledged and entered.

Applicant's arguments in paper No: 15 have been considered but are found not to be persuasive for the following reasons:

Rejection remains, because there is no disclosure in the claims 1-2, 6, 13, 15-16 which amino acid sequence of the TAFII105 polypeptide of SEQ ID NO:2 has a dominant negative effect on the normal biological activity of SEQ ID NO:2. Thus the claims encompass unrelated sequence with unknown structure, provided that it has a dominant negative effect on the normal biological activity of SEQ ID NO:2.

Further, concerning claims 20-21, since there is no definition of what is a polypeptide fragment "corresponding" to amino acids 443-552 of SEQ ID NO:2, one would not know how to determine which polypeptide fragment "corresponds" to amino acids 443-552 of SEQ ID NO:2.

2) Claims 13a, 15-16, 18-19 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a "pharmaceutical composition" comprising a cDNA

sequence encoding a fragment of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the normal biological activity of SEQ ID NO:2 for reasons already of record in paper No:14 .

Applicant argues that considerations regarding the therapeutic benefit or pharmaceutical aspect, i.e. "fully safe and efficacious" is more properly left to the FDA.

Concerning correlation between *in vitro* and *in vivo* for inducing apoptosis in cancer cells or inflammation cells, Applicant submits a Declaration by Dr. Dikstein, in which Dr. Dikstein recites that the cells used in the experiments described in the specification, i.e. 293 and Hela cell lines, are standard, internationally recognized modes for developing *in vivo* cancer treatments. In the Declaration, Dr. Dikstein also recites a reference by Silkow, A et al, 2002, which, consistent with the disclosure *in vitro*, teaches that in a transgenic mouse model system expressing the fragment TAFII105 C, said fragment inhibits transcriptional activation of NF-kB dependent anti-apoptotic genes. Applicant recites the reference by Van Antwerp, GJ et al, 1996 and Beg, AA et al, 1996, and argues that similarly, the involvement of NF-kB in anti-apoptotic gene activation in response to the TNF cytokine has been shown *in vitro* and confirmed *in vivo*.

The submission of the Declaration by Dr. Dickstein and the recitation of the references by Silkow, A et al, and Van Antwerp,GJ et al are acknowledged and entered.

Applicant's arguments in paper No: 15 have been considered but are found not to be persuasive for the following reasons:

It is noted that the issue of safety is not recited by the Examiner, nor is the issue of "fully efficacy", e.g. curing cancer, of the pharmaceutical use of the claimed fragment.

It is noted that in the transgenic mice expressing the fragment TAFII105 C consisting of amino acids 1-552 of SEQ ID NO:2, said fragment inhibits transcriptional activation of NF-kB dependent anti-apoptotic gene A20, whereas other survival genes such as bcl-2 and bcl-XL are not affected by said fragment (Silkow, A et al, 2002, p.17825, second column, last paragraph, bridging second column, first paragraph of p.17826).

The transgenic mice model would not be a representative model for treating cancer because the fragment of the polypeptide TAFII105 encoded by the claimed polynucleotide does not have any effect on bcl-2 or bcl-XL, as taught by Silkow et al, *supra,* which are known to be anti-apoptotic proteins, and could enhance cell survival and thus counteract the apoptotic activity of the claimed fragment, and because, different from cancer cells, the transgenic mice do not have cancer and do not over-express anti-apoptotic protein as in cancer cells. It is well known in the art that different from normal cells, cancer cells could overexpress anti-apoptic proteins such as Bcl-2 which suppresses apoptosis. For example, Schimmer, AD, 2003, Cancer Res, 63(6): 1242-8 teach that cancer cells such as leukemia could overepxress endogenous inhibitors of the effector caspases, such as antiapoptotic protein Bcl-2 and block the caspase pathways (abstract and p.1242, second column, first three lines).

Thus one would not expect that the claimed fragment could be used for treating cancer, because homeostasis is well known in the art (Oltvai et al, of record), and bcl-2

or bcl-XL could counteract the apoptotic effect of the fragment of the polypeptide TAFII105 encoded by the claimed polynucleotide, and because cancer treatment is unpredictable, as overwhelmingly taught by Gura, Jain, Curti, and Hartwell et al, all of record, and further because gene therapy is unpredictable, as taught by Miller, Deonarain, Verma and Crystal, all of record.

Concerning treatment of inflammation, it is noted that not only gene therapy is unpredictable, *supra*, but also the specification contemplates preventing apoptosis in inflammatory processes, which is the opposite effect of induction of apoptosis by the fragment of the polypeptide TAFII105 encoded by the claimed polynucleotide.

3. Claims 12, 13b remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for an antisense of SEQ ID NO:1 or a part thereof, which is capable of inhibiting expression of SEQ ID NO:1 *in vivo*, or a "pharmaceutical composition" comprising said antisense sequence, for reasons already of record in paper No: 14.

Applicant argues that in vitro use of cell lines for antisense treatments for animal or human cancers are well known in the art as a model that is predictive for subsequent animals or humans use. Applicant further argues that according to MPEP 608(p), the utility of a pharmaceutical could be shown by clinical or in vivo or in vitro evidence, or any combination.

Applicant further argues that many US patents have issued the use of antisense oligos, which would appear to contradict the Examiner position regarding the unpredictability of antisense oligos.

Applicant's arguments in paper No: 15 have been considered but are found not to be persuasive for the following reasons:

Contrary to Applicant's arguments, although in vitro use of cell lines for antisense treatments for animal or human cancers are well known in the art, they are not models for in vivo human or mouse treatment of cancers. It is well known in the art that antisense gene therapy is highly unpredictable. For example, Wang et al, of record, teach that therapeutic applications of antisense oligonucleotides are limited by their low physiological stability, slow cellular uptake resulting in insufficient delivery of adequate quantities of antisense oligonucleotides, and lack of tissue specificity. Similarly, Gura, of record, teaches difficulty getting antisense oligonucleotides to target tissues, and potential sides effects of antisense oligonucleotides.

Further, it is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Moreover, although many US patents have issued the use of antisense oligos, this does not make the claimed invention enabled, nor does this make the use of in vivo antisense oligonucleotides for cancers treatment predictable, because different applications are different and are not related to each other concerning their enablement issues, e.g. the presence of examples that enable the claimed in vivo treatment of a specific disease.

REJECTION UNDER 35 USC 102(b or e)

Claims 1-2, 13(c), 15-16 remain rejected under 35 USC 102 (b) as being anticipated by Dikstein, R et al, as evidenced by US 5,710,025. New claims 20-21 are rejected for the same reasons of record.

Applicant argues that neither reference teach a cDNA consisting of a sequence encoding a fragment of the TAFII105 polypeptide wherein the fragment has a dominant negative effect on the normal biological activity of the TAFII105 polypeptide. Applicant assertst that the full length TAFII105 polypeptide does not function in a dominant negative manner.

Applicant's arguments in paper No: 15 have been considered but are found not to be persuasive for the following reasons:

It is noted that that the specification discloses that the N-terminal amino acids 1-552 has dominant negative effect on the normal biological activity of the TAFII105 polypeptide.

Dikstein, R et al teach the polypeptide fragment of amino acids 1-552 of the human TAFII 105 sequence.

Thus the inherent nucleic acid sequence encoding the polypeptide fragment of amino acids 1-552 of the human TAFII 105 sequence, taught by Dikstein, R et al seems to be the same as the claimed fragment, in view that the nucleic acid sequence encoding the TAFII105 polypeptide is known in the art, as taught by US 5,710,025.

The reference does not specifically teach that the nucleic acid encodes a fragment that has a dominant negative effect on the normal biological activity of the TAFII105 protein. However, the claimed nucleic acid sequence appears to be the same as the prior art nucleic acid sequence. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Further, the inherent nucleic acid encoding the fragment taught by Dikstein, R et al seems to be the same as the claimed fragment of claims 20-21, since there is no definition of what is a polypeptide fragment "corresponding" to amino acids 443-552 of SEQ ID NO:2, and since the fragment taught by Dikstein, R et al seems to "correspond" to the amino acids 443-552 of SEQ ID NO:2 in claims 20-21.

The reference does not specifically teach that the nucleic acid encodes a fragment "corresponding" to amino acids 443-552 of the TAFII105 protein of SEQ ID NO:2. However, the claimed nucleic acid sequence appears to be the same as the prior art nucleic acid sequence. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

October 31, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER